www.nature.com/clinicalpractice/gasthep

Therapy Insight: drugs for gastrointestinal disorders in pregnant women

Chandrashekhar Thukral and Jacqueline L Wolf*

SUMMARY

The management and treatment of gastrointestinal ailments in pregnant women requires special attention and expertise, since the safety of the mother, fetus and neonate remains the primary focus. Nausea and vomiting during pregnancy is common, as is symptomatic gastroesophageal reflux disease. Peptic ulcer disease occurs less frequently and with fewer complications. Gastroenterologists and obstetricians should be familiar with safe treatment options for these conditions, because they can profoundly impair the quality of life of pregnant women. During pregnancy, constipation can develop *de novo*, or chronic constipation can increase in severity. Given the array of therapies for constipation, physicians must apprise themselves of drugs that are safe for both mother and fetus. Management of acute, self-limited diarrhea should focus on supportive therapy, dietary changes and maintenance of hydration. Treatment of chronic diarrhea should be considered in the context of therapy for the underlying disorder. Inflammatory bowel disease and irritable bowel syndrome present a unique therapeutic challenge—to control the disease while minimizing toxicity to the fetus and mother. Initiation and alteration of medical therapy for gastrointestinal disorders during pregnancy must be undertaken after discussion with the patient's obstetrician.

KEYWORDS gastroesophageal reflux disease, inflammatory bowel disease, irritable bowel syndrome, peptic ulcer disease, pregnancy, nausea and vomiting

REVIEW CRITERIA

PubMed was searched in April 2005 and December 2005 for articles published between January 1970 and December 2005, containing the terms "pregnancy and nausea and vomiting", "pregnancy and inflammatory bowel disease", "pregnancy and irritable bowel syndrome", "pregnancy and constipation", "pregnancy and diarrhea", "pregnancy and gastroesophageal reflux disease", "pregnancy and peptic ulcer disease", and "pregnancy and drug safety". Review articles were searched for pertinent publications within the same time frame. Abstracts presented at Digestive Disease Week 2005 were searched for relevant information. Manufacturers of some branded drugs were contacted for additional information.

JL Wolf is an Attending Physician in the Division of Gastroenterology, Beth Israel Deaconess Medical Center, and an Associate Professor of Medicine, Harvard Medical School; C Thukral is a Fellow in the Division of Gastroenterology, Beth Israel Deaconess Medical Center and a Clinical Teaching Fellow, Harvard Medical School, Boston, MA, USA.

Correspondence
*Division of Gastroenterology, Beth Israel Deaconess Medical Center, Rabb 437, 330 Brookline Avenue, Boston, MA 02215, USA
jwolf1@bidmc.harvard.edu

Received 9 September 2005 **Accepted** 1 February 2006

www.nature.com/clinicalpractice
doi:10.1038/ncpgasthep0452

INTRODUCTION

During pregnancy, the presence of gastrointestinal disease (that might be pre-existent to pregnancy or develop *de novo*) presents special challenges to the clinician. Drug therapy requires careful assessment and consideration before conception (for those with pre-existent disease), during pregnancy and in the postpartum period. The focus of therapy has to be guided by the dictum "first, do no harm", but this must sometimes be achieved by overcoming the instinct to delay or withhold treatment that could potentially produce an adverse outcome for the mother or the fetus.

The safety of drugs used in pregnancy has been assessed in animal studies, trials in pregnant women, and postmarketing studies. Unfortunately, because of the absence of prospective, controlled trials in pregnant women, there are limited data on the safety of many medications used to treat gastrointestinal disease during pregnancy. In addition, the safety of drugs in animal studies does not necessarily correlate with their safety in pregnant women, but often is the best information available. The current FDA categories for drug use during pregnancy are defined in Table 1. Other important resources on drug safety during pregnancy can be found on various websites.[1–3] Tables 2–6 summarize dosage and safety information on the drugs commonly used to treat various gastrointestinal ailments during pregnancy.

The most commonly encountered gastrointestinal diseases in pregnancy include nausea and vomiting in pregnancy (NVP), hyperemesis gravidarum, gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). The treatment of these diseases in pregnant women is discussed below.

NAUSEA AND VOMITING IN PREGNANCY

Nausea and vomiting in pregnancy (NVP) is common, occurring in 50–90% of women.[4] NVP is far more common in the first trimester than in

Table 1 Current FDA categories for drug use during pregnancy.[a]

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities in any trimester of pregnancy
B	Animal studies have revealed no evidence of harm to the fetus, but there are no adequate and well-controlled studies in pregnant women **OR** Animal studies have shown an adverse effect on the fetus, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester
C	Animal studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in pregnant women **OR** No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women
D	Adequate well-controlled or observational studies in pregnant women have demonstrated a risk to the fetus; however, the benefits of therapy could outweigh the potential risk. For example, use of the drug might be acceptable in a life-threatening situation or to treat a serious disease for which safer drugs cannot be used or are ineffective
X	Adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities or risks. The use of the product is contraindicated in women who are or might become pregnant

[a]Adapted from reference 63.

the third trimester and occurs more frequently in women who have multiple gestations compared with women who have a single gestation.[4] A number of therapies have been investigated in the treatment of NVP (Table 2).

Vitamin B_6

Vitamin B_6 (pyridoxine hydrochloride; category A), administered at a dose of 10–25 mg three times daily, was shown to improve NVP in two small studies.[5,6]

Doxylamine

Doxylamine (category B), an antihistamine that has been used with some success to treat severe nausea and vomiting, is available in two preparations: as doxylamine succinate alone or in combination with pyridoxine hydrochloride (Diclectin®, Duchesnay Inc., Laval, QC, Canada; Bendectin®, Merrell Dow Pharmaceuticals, US).[4] Bendectin® (also known as debendox and lenotan) was withdrawn from the US market because of concerns about possible teratogenicity, although a subsequent meta-analysis revealed no association between Bendectin® and birth defects.[7] Diclectin® is used to treat NVP in Canada (the only country in which it is available). A study of 225 patients treated with high-dose Diclectin® (5–12 tablets per day) and two meta-analyses of doxylamine revealed no increase in fetal congenital malformations.[7,8]

Antiemetics

Antiemetics also offer symptomatic relief in patients with NVP.[9] The safety of the phenothiazines, promethazine and prochlorperazine (both category C), have not yet been proven; however, they are widely used in pregnancy.[4] Metoclopramide (category B) is frequently used for the treatment of NVP, and seems to be safe in pregnancy.[10] Although there is limited experience using ondansetron for NVP, available studies do not indicate any increased risk of fetal malformations with its use during pregnancy.[11]

HYPEREMESIS

In contrast to NVP, hyperemesis gravidarum is a serious condition characterized by severe vomiting that can result in dehydration and weight loss, necessitating parenteral or enteral nutrition. It occurs most commonly in the first trimester and in patients who are overweight, multiparous or have had multiple gestations.[12] At present, there are very few evidence-based data to support a particular pharmacologic treatment in hyperemesis gravidarum (Table 2). Management involves symptomatic treatments for severe nausea and vomiting, as well as correction of dehydration and electrolyte abnormalities. In severe cases, patients might also benefit from enteral or parenteral nutrition.[4]

From an alternative-medicine standpoint, a recent randomized trial showed that acupuncture

Table 2 Summary of drugs commonly used for nausea and vomiting in pregnancy and hyperemesis gravidarum during pregnancy.

Drug	Pregnancy use category	Usual dosage	Additional comments[a]
Vitamin B_6	A	10–25 mg three times daily	—
Doxylamine	B	12.5 mg twice daily	Available alone or in combination with vitamin B_6 (Diclectin®; only available in Canada)
Prochlorperazine	C	5–10 mg three times daily	Unproven safety but widely used
Promethazine	C	12.5–25.0 mg four times daily	Unproven safety but widely used
Metoclopramide	B	10–20 mg four times daily	Seems safe for use
Ondansetron	B	4–8 mg three times daily	Seems safe but based on limited data

[a]Please see text for references.

Table 3 Summary of drugs commonly used for gastroesophageal reflux disease and peptic ulcer disease during pregnancy.

Drug	Pregnancy use category	Usual dosage	Additional comments[a]
Magnesium and aluminum hydroxide	B	10–30 ml as needed	In normal therapeutic doses, most antacids that contain magnesium, calcium or aluminum are considered safe
Sucralfate	B	1 g 1 h before meals and at bedtime	—
H2 blockers	B	Dose differs according to retail brand	—
Proton-pump inhibitors	B (C)	Dose differs according to retail brand	All proton-pump inhibitors except omeprazole (category C) are classified as category B

[a]Please see text for references.

was as effective as metoclopramide plus vitamin B_{12} therapy for symptomatic relief in pregnant women with hyperemesis gravidarum, and was significantly more effective than this drug regimen in improving functional status.[13]

Corticosteroids

Corticosteroids (category B) have been used to treat women with severe hyperemesis, although the mechanism of their action is not well understood.[4] Although corticosteroid therapy is generally considered safe during pregnancy, a recent meta-analysis demonstrated a marginally increased risk of major congenital malformation and a 3.4-fold increased risk of oral cleft in infants who had been exposed to corticosteroids in the first trimester.[9]

Erythromycin

Erythromycin (category B), which stimulates gastric motility by binding to the motilin receptor, improved the symptoms of hyperemesis gravidarum in two case reports, when administered orally for 5 days.[4] Although large studies do not support an association between erythromycin and congenital malformations, it is rarely used to treat hyperemesis gravidarum.[14]

GASTROESOPHAGEAL REFLUX DISEASE AND PEPTIC ULCER DISEASE

Symptomatic GERD is commonly reported in pregnancy, with 40–80% of women experiencing reflux. The condition usually begins in the first or second trimester and generally persists throughout pregnancy, with significant improvement following delivery.[15] Symptoms of GERD are similar in pregnant and nonpregnant women and complications are uncommon in pregnancy. PUD, on the other hand, occurs less frequently, with fewer complications and with less-severe symptoms in pregnant women.[16]

There are no published, controlled trials on the management of GERD and PUD during pregnancy. Most medications used in the management of these disorders are considered to be safe, on the basis of case reports and retrospective cohort studies (Table 3).

Initial treatment of GERD consists of conservative measures, such as the avoidance of foods and other substances that might provoke reflux

symptoms in the individual patient. In particular, the patient should be advised to avoid fatty foods, citrus juices, caffeine, chocolate, mint, nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, and smoking. Nocturnal reflux symptoms can sometimes be alleviated by elevating the head of the bed by 15 cm at night-time, and by decreasing food and fluid intake within 4 h of bedtime. When symptoms are refractory to these interventions then a trial of medical therapy is appropriate.[15] Since the dyspeptic symptoms of GERD and PUD tend to overlap, it is reasonable to apply a similar, stepwise approach for treatment of PUD during pregnancy.[17]

Esophagogastroduodenoscopy is recommended during pregnancy for the diagnosis of suspected PUD only when symptoms are severe and refractory to intensive medical therapy, or in the setting of PUD-associated complications, such as hemorrhage or gastric-outlet obstruction.

Antacids

Antacids are commonly used for the treatment of GERD and PUD, and are felt to be safe in pregnancy. Of the antacids available, those containing bicarbonate should be avoided, as they can precipitate metabolic alkalosis in the mother and fetus.[17] Most antacids containing magnesium, calcium or aluminum, in normal therapeutic doses, are considered acceptable during pregnancy.[17,18] The safety and efficacy of these antacids were demonstrated by Land and Dougall who demonstrated that 50% of pregnant women achieved relief of reflux symptoms within 2 weeks of using magnesium-containing or aluminum-containing antacids, without any increase in congenital anomalies in newborn babies.[19] Sucralfate (category B), an aluminum-containing sulfated polysaccharide complex that promotes ulcer healing, is safe and poses no risk to the fetus.[20]

H2 blockers

In patients with more-severe symptoms who have not responded to antacid therapy, histamine-2 receptor antagonists (also known as H2 blockers) are often effective in controlling symptoms of reflux and promoting ulcer healing. The H2 blocker that has been in longest use, cimetidine, has demonstrated safety in several large follow-up and registry studies.[17] A surveillance study of over 200,000 Medicaid recipients in Michigan, US, found no increase in congenital anomalies among newborn babies who were exposed to H2 blockers during the first trimester *in utero*, including 460 neonates exposed to cimetidine, 516 neonates exposed to ranitidine, and 33 neonates exposed to famotidine.[14] Similarly, nizatidine has not been shown to cause congenital anomalies.[20] Cimetidine, ranitidine, famotidine and nizatidine are all classified as category B drugs during pregnancy.[17]

Proton-pump inhibitors

Proton-pump inhibitors (PPIs) have been shown to be effective in the treatment of GERD, esophagitis and PUD. Although generally regarded as safe in pregnancy, extensive clinical data on the use of these agents in pregnant patients do not exist. Studies of omeprazole (category C) in laboratory animals have demonstrated its lethality for embryos.[14] Large registry studies, however, such as the Swedish Medical Birth Registry, did not demonstrate any increase in congenital defects.[17] Registry studies and case reports have demonstrated that lansoprazole, rabeprazole, pantoprazole and esomeprazole are safe in pregnancy, and all of these drugs are characterized as category B drugs during pregnancy.[14,15]

Helicobacter pylori eradication therapy

Treatment of *Helicobacter pylori* infection with triple drug regimens consisting of antibiotics and PPI therapy should be avoided during pregnancy, because the risk of complications from untreated *H. pylori* infection is low in the short term, and because of the success of acid-suppressing therapy for controlling symptomatic PUD, and the potential teratogenicity or other fetal side effects of certain antibiotics used in these regimens. While ulcer treatment with H2 blockers and PPI therapy can be offered to alleviate symptoms and promote ulcer healing, multidrug therapy for *H. pylori* infection is best deferred until the postpartum period.[17]

Bismuth subsalicylate

Bismuth subsalicylate (Pepto-Bismol®, Procter & Gamble, Cincinnati, OH; category C) is hydrolyzed in the gastrointestinal tract to inorganic bismuth salts that are poorly absorbed and salicylates that are readily absorbed. Although bismuth has not been reported to cause abnormalities in human fetuses, chronic administration of bismuth tartrate to lambs resulted in poor outcomes.[17] In addition, chronic ingestion of salicylates by mothers has

Table 4 Summary of drugs commonly used for constipation during pregnancy.

Drug	Pregnancy use category	Usual dosage	Additional comments[a]
Polyethylene glycol	C	17 g daily, taken with 240 ml water	Limited data in pregnant women; considered safe
Lactulose	B	15–30 ml up to four times daily	Use often limited by cramping and bloating
Senna	C	2 tablets daily; maximum dose 4 tablets twice daily	Safe and effective in pregnancy; each tablet contains 8.6 mg of sennosides
Bisacodyl	B	5–15 mg as needed	Use limited by cramping

[a]Please see text for references.

resulted in congenital defects, premature closure of the ductus arteriosus *in utero*, and intrauterine growth retardation.[21] For these reasons, bismuth subsalicylate should be avoided in pregnancy.

CONSTIPATION

Even though it is commonly believed that constipation is a frequent complaint in pregnancy, the clinical data regarding its incidence are equivocal. Constipation can occur *de novo* during pregnancy, or chronic constipation can increase in severity during pregnancy. The safety of drug therapy for constipation in pregnancy has not been thoroughly evaluated, but most standard therapeutic regiments seem to be safe (Table 4).[21] Although many women attribute some of their constipation to use of prenatal vitamins that contain iron, the vitamins should be continued if at all possible.

Bulk-forming laxatives

Dietary modification, through increased fiber intake and ensuring adequate liquid consumption, should be the first-line therapy for constipation in pregnancy. Supplementation of fiber ingested in the diet with bulk-forming laxatives such as psyllium, methylcellulose, guar, calcium polycarbophil, pectin, and/or flax seed (ground or whole) to 25–40 g/day of fiber is safe and often effective.[21] Bloating can occur with some sources of fiber, but not others: if bloating occurs, changing the source of fiber might be beneficial.[22] Although the use of stool softeners such as docusate in pregnancy has not been associated with congenital defects, their efficacy is questionable.[23]

Hyperosmolar laxatives

Polyethylene glycol, the nonabsorbable sugars such as lactulose and sorbitol, and glycerin are all hyperosmolar laxatives that can be safely used during pregnancy if dietary manipulation fails.[24,25] A prospective study in 40 pregnant women with constipation found that treatment with 250 ml of polyethylene glycol 4000 significantly increased the number of evacuations, from 1.66 to 3.16 per week.[25] The pain experienced by the patients also improved, and 73% of the women had resolution of their constipation. The use of nonabsorbable sugars, however, is often limited by bloating and cramping. Saline hyperosmotic laxatives, such as phosphorus salts (Fleet Phospho-Soda®, CB Fleet Company Inc., Lynchburg, VA) and magnesium-containing laxatives can result in sodium retention in the mother, and are best avoided.[21]

Lubricant laxatives

Use of the lubricant laxative mineral oil should be limited to short periods, because of the possibility of malabsorption of vitamins and nutrients.[21] Oral administration should be avoided in patients with impaired swallowing, because of the risk of developing aspiration pneumonia.[26]

Stimulant laxatives

It is reasonable to consider use of stimulant laxatives, if osmotic and bulk laxatives fail to relieve the constipation. The stimulant laxatives senna and bisacodyl seem to be safe in pregnancy and have not been reported to be teratogenic.[27] Oral bisacodyl often produces cramping, which limits its use.[26] Stimulant laxatives such as castor oil can induce uterine contractions in the mother and should be avoided.[21]

ACUTE DIARRHEA

The pathogenesis and differential diagnosis of acute diarrhea in pregnant women is similar to that in their nonpregnant counterparts. Most cases of acute, self-limited diarrhea are caused by viruses, bacteria and their toxins, or parasites.

Table 5 Summary of drugs commonly used for irritable bowel syndrome and diarrhea during pregnancy.

Drug	Pregnancy use Category	Usual dosage	Additional comments[a]
Tegaserod	B	6 mg twice daily	Limited data; should be considered only when other measures fail to control constipation-predominant irritable bowel syndrome
Loperamide	B	2–4 mg daily or after each unformed stool	Antidiarrheal agent of choice during pregnancy
Diphenoxylate with atropine sulfate	C	1–2 tablets four times daily	Should be avoided during pregnancy. Contains 2.5 mg diphenoxylate plus 0.025 mg atropine per tablet
Dicycloverine (dicyclomine)	B	10–20 mg four times daily	Should be reserved for women with refractory symptoms
Hyoscyamine	C	0.125–0.250 mg every 6 h as needed	Should be reserved for women with refractory symptoms
Tricyclic antidepressants	C/D	Dose differs according to retail brand	Questionable safety in pregnancy; use should be limited to the severely symptomatic

[a]Please see text for references.

Noninfectious causes of diarrhea include food intolerances and ingestion of osmotic agents, as well as chronic conditions such as functional disorders and IBD.[28] The specific cause of infectious diarrhea need not be pursued unless the illness is prolonged for more than 7 days, the person has significant rectal bleeding or is extremely ill. Uncomplicated cases can, therefore, be treated with a focus on supportive therapy in the form of correction of fluid losses and electrolyte abnormalities, dietary changes and maintenance of hydration.[29] If symptoms remain persistent, limited use of antidiarrheal agents, as outlined below, can be considered (Table 5).

Loperamide (category B) is the antidiarrheal drug of choice during pregnancy. It is a peripherally acting opiate-receptor agonist that increases intestinal ion and water absorption, decreases intestinal transit by relaxing localized and segmental colonic spasms, and strengthens anal sphincter tone.[29] A study of 105 women who had used loperamide during the first trimester of pregnancy showed no increase in minor or major birth defects of the fetus when compared with control women, although 21 of the babies were 200 g smaller than the babies born to women in the control group.[30] Use of diphenoxylate combined with atropine sulfate (category C) during the second or third trimester was found to be teratogenic in animals and, therefore, should be avoided during pregnancy in humans.[31]

Bismuth subsalicylate, as discussed previously, should be avoided in pregnancy.

IRRITABLE BOWEL SYNDROME

IBS is common in women of childbearing age and the effect of the pregnancy on IBS and the safety of IBS drugs in pregnancy are important to understand. As there are no large studies that have followed women with IBS through pregnancy, it is not known whether women require the same or a modified therapeutic regimen during pregnancy. Some interventions are safer than others (Table 5) and, therefore, it is important to consider the benefits and risks when treating a woman with IBS who is gravid or trying to conceive.[14,30]

Treatments for constipation

Constipation in a pregnant woman with IBS should be treated as discussed in the section on constipation. Tegaserod (category B) is approved for treatment of constipation-predominant IBS in women for up to 12 weeks. Although the drug has not produced any ill effects on pregnant animals, experience is very limited in pregnant and nursing women.[32] It should, therefore, be used only when other measures fail to control severe symptoms of constipation in pregnant IBS patients.

Treatments for diarrhea

Diarrhea does not usually respond to dietary manipulation. During pregnancy women often increase lactose ingestion, and those who are lactose intolerant consequently develop diarrhea, bloating, and/or abdominal pain. In these women, limitation of lactose intake and calcium supplementation might be therapeutic.

Use of the antidiarrheal agents loperamide and diphenoxylate is discussed in the preceding section. Colestyramine (category C), a bile-acid sequestrant, can be used as an antidiarrheal drug, but can potentially cause malabsorption of fat-soluble vitamins if used in large doses for prolonged periods of time.[33]

Antispasmotic medications

Antispasmotic medications are frequently given to patients with IBS before pregnancy. Their efficacy in pregnancy, however, has not been adequately assessed. Dicycloverine (dicyclomine) (category B) does not seem to pose a problem to the mother or fetus, as shown by the Michigan Medicaid recipient surveillance study, which did not indicate an increased occurrence of birth defects, except perhaps for polydactyly, in babies born to women who had taken dicycloverine.[14] In addition, hyoscyamine (category C), although not well studied, has not been shown to have adverse effects in pregnant women.[14] Given the lack of substantive safety data, the use of antispasmodic agents should be reserved for pregnant women with IBS whose symptoms are refractory to other, more conservative, treatments.[30]

Tricyclic antidepressants

Tricyclic antidepressants are commonly prescribed for nonpregnant women with IBS. Amitriptyline and nortriptyline are both category D drugs in pregnancy. Their assignment to this category seems to stem from a report of limb abnormalities in animals and humans.[14] Subsequent investigation of infants born to mothers exposed to tricyclic antidepressants before and during pregnancy did not confirm an increase in congenital malformations.[34] Urinary retention in neonates has been associated with nortriptyline use during pregnancy in the mother.[14] Desipramine (category C) has not been shown to cause limb abnormalities or other birth defects but its use in pregnancy has been associated with withdrawal symptoms in newborn babies.[34] Overall, the safety of the tricyclic antidepressants in pregnancy is still questionable, and their use should be limited to the severely symptomatic patient.[30]

Selective serotonin reuptake inhibitors

The selective serotonin reuptake inhibitors (SSRIs) (category C) have been used in women with IBS and depression. The main concern with their use in pregnant women is a possible increase in spontaneous abortions in women exposed to fluoxetine or paroxetine early in pregnancy.[30] Subsequent evaluation of 267 women exposed to the SSRIs fluvoxamine, paroxetine or sertraline did not show an increased risk of miscarriage, fetal malformations or prematurity.[35] A neonatal behavioral syndrome linked to *in utero* exposure to SSRIs during the third trimester has, however, recently been identified. This self-limited syndrome, the long-term sequelae of which are as yet unknown, is characterized by central nervous system, motor, respiratory, and gastrointestinal signs, and is noted mostly in cases involving fluoxetine and paroxetine exposures. The FDA and the manufacturers of SSRIs recently agreed to a labeling change for this class of drugs that cautions physicians and patients about the neonatal complications associated with late pregnancy exposure.[36] As with tricyclic antidepressants, these drugs should only be considered for the severely symptomatic pregnant IBS patient, keeping in mind the potential for precipitating this self-limited behavioral syndrome in neonates. The safety and efficacy of alternative treatment modalities for IBS in pregnant women is unknown.

INFLAMMATORY BOWEL DISEASE

Many studies of women with Crohn's disease and ulcerative colitis indicate that the outcome of pregnancy depends on the activity of the IBD. The presence of active IBD in pregnant women increases the risk of pregnancy complications, including preterm delivery and low birth weight. By contrast, women with IBD who remain in remission during pregnancy are likely to have an uncomplicated pregnancy.[37–39] Patients with IBD should, therefore, be advised to defer pregnancy until their disease is in remission, but the optimal duration of remission before conception remains unclear.

Disease activity during pregnancy seems to correlate with disease activity at the time of conception. Pregnancy does not seem to increase the rate of relapse in women with quiescent ulcerative colitis or Crohn's disease, whereas active IBD at the time of conception is likely to remain active, and possibly worsen, during the course of pregnancy.[39,40] Relapses occur most commonly during the first trimester for ulcerative colitis, and in the first and second trimester and puerperium for Crohn's disease.[41,42]

Table 6 Summary of drugs commonly used for inflammatory bowel disease during pregnancy.

Drug	Pregnancy use category	Usual dosage	Additional comments[a]
5-aminosalicylic acid	B	Dose differs according to retail brand	Sulfasalazine and mesalamine (also known as mesalazine) can be used safely in oral and topical forms. Olasalazine is the only 5-aminosalicylic acid drug categorized as Class C
Corticosteroids	B	Variable	Effective in inducing but not maintaining remission
Budesonide	C	9 mg daily	Probably safe for use in patients with ileo-colonic Crohn's disease but no controlled studies are available in pregnant women
Infliximab	B	5–10 mg/kg intravenous	Seems safe based on limited data
6-mercaptopurine/ azathioprine	D	Starting at 50 mg	Use is justified if patient has active disease refractory to other oral or topical agents. Possibly minimal teratogenicity in human fetuses
Ciclosporin	C	Weight-based intravenous dosing	Use justified if patient has active disease refractory to other oral or topical agents. Can cause small-for-gestational-age births
Metronidazole	B	250–500 mg three times daily	Seems safe during pregnancy but use is limited to second and third trimesters because of potential mutagenicity in the first trimester
Fluoroquinolones	C	Dose differs according to retail brand	Limited safety data; usually avoided during pregnancy owing to possible effects on collagen development
Methotrexate	X		Contraindicated in pregnancy owing to teratogenicity

[a]Please see text for references.

Medical management of IBD during pregnancy should be guided by the principle that active disease, rather than treatment for disease, poses the greatest risk to the pregnancy. Owing to a lack of prospective studies in pregnant women, there are limited data on the safety of medications used to treat IBD in pregnancy. Most medications used for the treatment of IBD in the general population, however, seem to be safe in pregnancy (Table 6). Symptomatic treatments for IBD patients include antidiarrheal, antispasmodic, and analgesic agents (see IBS section).

Aminosalicylates

Aminosalicylates including sulfasalazine (category B), mesalazine (mesalamine; category B), and newer 5-aminosalicylic acid (5-ASA) agents are the mainstay of treatment for ulcerative colitis and also have an important role in the management of Crohn's disease. Sulfasalazine has been used for treatment of IBD for more than 50 years, and several large studies have demonstrated the safety of sulfasalazine during pregnancy.[42] Patients receiving sulfasalazine should receive folate supplementation to decrease the risk of neural-tube defects.[42] Prospective studies have shown that mesalamine and other 5-ASA agents, in both oral and topical forms, can be used safely in pregnancy. Olsalazine is the only 5-ASA agent that is categorized as a class C drug.[43–45]

Corticosteroids

In IBD patients with moderate disease activity, topical and oral corticosteroids (category B) are effective in inducing remission. These agents, however, have no role in the maintenance of remission. Corticosteroids are generally considered safe during pregnancy (category B). In a large series of pregnant women with IBD who were treated with steroids, there was no increase in congenital anomalies or in the incidence of prematurity, spontaneous abortion, or stillbirths.[46] Use of shorter-acting agents such as prednisone, prednisolone, and methylprednisolone is preferable, as these agents are metabolized by placental enzymes, resulting in fetal exposure levels of only 10% of the maternal dose.[47]

A newer oral corticosteroid, budesonide, undergoes extensive first-pass hepatic metabolism and can be used for patients with Crohn's

disease affecting the ileum or right colon.[48] Budesonide has fewer steroid side effects compared with other glucocorticoids, because it has topical anti-inflammatory activity but low systemic activity. A lack of controlled studies in pregnant women, however, means that budesonide is classified as a pregnancy category C drug.[49]

Immunomodulators

In steroid-dependent patients who are unresponsive to 5-ASA agents, immunomodulatory drugs such as 6-mercaptopurine (category D) and azathioprine (category D), are effective as maintenance therapy.[50] Although there is a lack of large studies evaluating the use of these agents for the treatment of IBD during pregnancy, retrospective studies indicate that they have no increased risk (or pose only a minor increase in risk) during pregnancy, and hence they can be used safely.[51,52] The use of these agents is justified if the patient has active disease that is refractory to other oral or topical agents.[47,53]

Significant controversy exists regarding the teratogenic effect of 6-mercaptopurine taken by fathers at the time of conception. A retrospective study found that the incidence of 6-mercaptopurine-related complications (spontaneous abortions, congenital anomalies, including missing thumb, acrania, and multiple digital and limb abnormalities) were increased when fathers had used 6-mercaptopurine less than 3 months before conception.[54] A separate study conducted in renal transplant patients, however, indicated that azathioprine and 6-mercaptopurine use by the father does not increase the risk of congenital anomalies.[55] These conflicting data mean that it is unclear whether azathioprine or 6-mercaptopurine should be withheld from fathers for 3 months before conception is planned.

Methotrexate (category X), which has a role in the treatment of refractory Crohn's disease, is contraindicated in pregnancy because of its abortifacient and teratogenic effects, which include craniofacial and limb defects, central nervous system abnormalities, and myelosuppression.[47]

Antibiotics

The available data on the safety of antibiotics for treatment of Crohn's disease in pregnancy are limited. While there are no studies assessing the safety of metronidazole (category B) in pregnancy for the treatment of Crohn's disease, a study of over 200 women who received metronidazole for vaginitis during the first trimester of pregnancy revealed no association with spontaneous abortions or congenital abnormalities.[56] Most clinicians, however, limit use of metronidazole to the second and third trimesters. Similarly, there are limited data on the safety of fluoroquinolones (category C) for treatment of IBD in pregnancy. A few reports indicate that fluoroquinolones are not teratogenic when used briefly during pregnancy;[57,58] however, there is concern that fluoroquinolones might cause cartilage deformities in the fetus, and no long-term follow-up is available to determine whether arthritis develops prematurely.[42]

Infliximab

Infliximab, a monoclonal antibody to tumor necrosis factor-α, was the first biologic agent approved for the treatment of refractory luminal or fistulizing Crohn's disease.[59] On the basis of over 100 reports and drug company data, infliximab seems to be safe in pregnancy, and it is therefore classified as a category B agent.[60,61] A recent report, however, showed high serum levels of infliximab at 6 weeks postpartum in an otherwise healthy, breastfed infant whose mother had been treated with the drug during pregnancy.[62] Infliximab could not be detected in breast milk, and the authors concluded that serum levels in the infant were the result of placental transfer. It might, therefore, be premature to draw any firm conclusions.

CONCLUSION

Pregnancy represents a unique state with physiologic changes that can have profound effects on pre-existent gastrointestinal diseases, as well as predisposing women to other specific gastrointestinal disorders. An important, yet often overlooked, concept is that every visit to a physician's office by a woman of reproductive age who has a chronic medical condition should be treated as a preconception visit. It is imperative to discuss the implications for a potential pregnancy of altering the current medication regimen, or initiating new therapy, with each patient. Similarly, once the patient finds out that she is pregnant, it is vital that she confer with her health-care providers about the safety, benefits and risks of her medications. In general, the safety of the mother, fetus and neonate remains the primary focus of all therapeutic interventions.

KEY POINTS

- Drug therapy requires careful assessment and consideration before conception (for those with pre-existent disease), during pregnancy, and in the postpartum period
- When considering therapeutic interventions, the safety of the mother, fetus and neonate has to be carefully balanced with overcoming the instinct to delay or withhold treatment that could potentially produce an adverse outcome

References

1 Reproductive Toxicology Center online information system [www.reprotox.org] (accessed 10 February 2006)
2 Motherrisk Online [www.motherisk.org] (accessed 10 Febrruary 2006)
3 California Teratogen Information Service pregnancy risk information [www.ctispregnancy.org] (accessed 10 Febrruary 2006)
4 Koch KL and Frissora CL (2003) Nausea and vomiting during pregnancy. *Gastroenterol Clin North Am* **32:** 201–234
5 Shahaklan V *et al.* (1991) Vitamin B_6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double blind, placebo-controlled study. *Obstet Gynecol* **78:** 33–36
6 Niebyl JR and Goodwin TM (2002) Overview of nausea and vomiting in pregnancy with an emphasis on vitamins and ginger. *Am J Obstet Gynecol* **186 (Suppl):** S253–S255
7 Atanackrovic G *et al.* (2001) The safety of higher than standard dose of doxylamine–pyridoxine (Diclectin) for nausea and vomiting of pregnancy. *J Clin Pharmacol* **41:** 842–845
8 McKeigue PM *et al.* (1994) Bendectin and birth defects: a meta-analysis of the epidemiologic studies. *Teratology* **20:** 27–37
9 Quinlan JD and Hill DA (2003) Nausea and vomiting of pregnancy. *Am Fam Physician* **68:** 121–128
10 Berkovitch M *et al.* (2000) Fetal effects of metoclopramide therapy for nausea and vomiting of pregnancy. *N Engl J Med* **343:** 445–446
11 Einarsen A *et al.* (2004) The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG* **111:** 940–943
12 Goodwin TM (2002) Nausea and vomiting of pregnancy: an obstetric syndrome. *Am J Obstet Gynecol* **186 (Suppl):** S184–S189
13 Neri I *et al.* (2005) Acupuncture versus pharmacological approach to reduce hyperemesis gravidarum discomfort. *Minerva Ginecol* **57:** 471–475
14 Briggs GG *et al.* (1998) *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk* edn 5. Baltimore: Williams & Wilkins
15 Richter JE (2003) Gastroesophageal reflux disease during pregnancy. *Gastroenterol Clin North Am* **32:** 235–261
16 Borum ML (1998) Gastrointestinal diseases in women. *Med Clin North Am* **82:** 21–50
17 Cappell MS (2003) Gastric and duodenal ulcers during pregnancy. *Gastroenterol Clin North Am* **23:** 263–308
18 Broussard CN and Richter JE (1998) Treating gastro-oesophageal reflux disease during pregnancy and lactation: what are the safest therapy options? *Drug Saf* **19:** 325–327
19 Land GD and Dougall A (1989) Comparative study of Algicon suspension and magnesium trisilicate mixture in the treatment of reflux dyspepsia of pregnancy. *Br J Clin Pract* **66 (Suppl):** 48–51
20 Charan K and Katz PO (2001) Gastroesophageal reflux disease in pregnancy. *Curr Treat Options Gastroenterol* **4:** 73–81
21 Wald A (2003) Constipation, diarrhea and symptomatic hemorrhoids during pregnancy. *Gastroenterol Clin North Am* **32:** 309–322
22 Wald A (2000) Constipation. *Med Clin North Am* **84:** 1231–1246
23 Schindler AM (1984) Isolated neonatal hypomagnesemia associated with maternal overuse of stool softener. *Lancet* **2:** 822
24 Lewis JH *et al.* (1985) The use of gastrointestinal drugs during pregnancy and lactation. *Am J Gastroenterol* **80:** 912–923
25 Neri I *et al.* (2004) Polyethylene glycol electrolyte solution (Isocolan) for constipation during pregnancy: an observational open-label study. *J Midwifery Womens Health* **49:** 355–358
26 Gatusso JM and Kamm MA (1994) Adverse effects of drugs used in the management of constipation and diarrhea. *Drug Saf* **10:** 47–65
27 Prather CM (2004) Pregnancy-related constipation. *Curr Gastroenterol Rep* **6:** 402–404
28 Bonapace ES and Fisher RS (1998) Constipation and diarrhea in pregnancy. *Gastroenterol Clin North Am* **27:** 197–211
29 Wolf J (1994) Acute diarrhea. In *Office Practice of Medicine*, 295–307 (ed WT Branch) edn 3. Philadelphia: WB Saunders
30 Hasler WL (2003) The irritable bowel syndrome during pregnancy. *Gastroenterol Clin North Am* **32:** 385–390
31 Lewis JH and Weingold AB (1985) The use of gastrointestinal drugs during pregnancy and lactation. *Am J Gastroenterol* **80:** 912–923
32 DeYoung GR (2004) Tegaserod (Zelnorm) for irritable bowel syndrome. *Am Fam Physician* **69:** 363–364
33 Latikainen T (1978) Effect of cholestyramine and phenobarbitol on pruritus and serum bile acid levels in cholestasis of pregnancy. *Am J Obstet Gynecol* **132:** 2020–2025
34 Misri S and Sivertz K (1991) Tricyclic drugs in pregnancy and lactation: a preliminary report. *Int J Psych Med* **21:** 157–171
35 Kulin NA *et al.* (1998) Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* **279:** 609–610
36 Eydie L *et al.* (2005) Neonatal signs after late *in utero* exposure to serotonin reuptake inhibitors. *JAMA* **293:** 2372–2383
37 Alstead EM and Nelson-Piercy C (2003) Inflammatory bowel disease in pregnancy. *Gut* **52:** 159–161
38 Baiocco PJ and Korelitz BI (1984) The influence of inflammatory bowel disease and its treatment on pregnancy and fetal outcome. *J Clin Gastroenterol* **6:** 211–216
39 Ferrero S and Ragni N (2004) Inflammatory bowel disease: management issues during pregnancy. *Arch Gynecol Obstet* **270:** 79–85
40 Miller JP (1986) Inflammatory bowel disease in pregnancy: a review. *J Royal Soc Med* **79:** 221–225
41 Nellsen OH *et al.* (1983) Pregnancy in ulcerative colitis. *Scand J Gastroenterol* **18:** 735–742
42 Kane S (2003) Inflammatory bowel disease in pregnancy. *Gastroenterol Clin North Am* **32:** 323–240
43 Habal FM *et al.* (1993) Oral 5-aminosalicylic acid for inflammatory bowel disease in pregnancy: safety and clinical course. *Gastroenterology* **105:** 1057–1060
44 Bell CM and Habal FM (1997) Safety of topical 5-aminosalicylic acid in pregnancy. *Am J Gastroenterol* **92:** 2201–2202

Acknowledgments
We would like to thank Dr Sarathchandra Reddy and Ms Jennifer Arich for their help in preparing this manuscript.

Competing interests
The authors declared they have no competing interests.

45 Diav-Citrin O *et al.* (1998) The safety of mesalamine in human pregnancy: a prospective controlled cohort study. *Gastroenterology* **114:** 23–28
46 Mogadam M *et al.* (1981) The course of inflammatory bowel disease during pregnancy and postpartum. *Am J Gastroenterol* **75:** 265–269
47 Janssen NM and Genta MS (2000) The effects of immunosupressive and anti-inflammatory medications on fertility, pregnancy, and lactation. *Arch Intern Med* **160:** 610–619
48 Papi C *et al.* (2000) Budesonide in the treatment of Crohn's disease: a meta-analysis. *Aliment Pharmacol Ther* **14:** 1419–1428
49 Navarro F and Hanauer SB (2003) Treatment of inflammatory bowel disease: safety and tolerability issues. *Am J Gastroenterol* **98 (Suppl):** S18–S23
50 Hanauer S (2004) Medical therapy for ulcerative colitis. *Gastroenterology* **126:** 1582–1592
51 Present D *et al.* (1989) 6-mercaptopurine in the management of inflammatory bowel disease: short and long-term toxicity. *Ann Intern Med* **11:** 641–649
52 Alstead EM *et al.* (1990) Safety of azathioprine in pregnancy in inflammatory bowel disease. *Gastroenterology* **99:** 443–446
53 Connell W and Miller A (1999) Treating inflammatory bowel disease during pregnancy: risks and safety of drug therapy. *Drug Saf* **21:** 311–323
54 Rajapakse RO *et al.* (2000) Outcome of pregnancies when fathers are treated with 6-mercaptopurine for inflammatory bowel disease. *Am J Gastroenterol* **95:** 684–688
55 Kane SV (2000) What's good for the goose should be good for the gander—6 MP use in fathers with inflammatory bowel disease. *Am J Gastroenterol* **95:** 581–582
56 Rosa FW *et al.* (1989) Pregnancy outcomes after first-trimester vaginitis drug therapy. *Obst Gyn* **69:** 751–755
57 Korelitz BI (1998) Inflammatory bowel disease and pregnancy. *Gastroenterol Clin North Am* **27:** 213–217
58 Berkovitch M *et al.* (1994) Safety of the new quinolones in pregnancy. *Obstet Gynecol* **84:** 535–538
59 Egan LJ and Sandborn WJ (2004) Advances in the treatment of Crohn's disease. *Gastroenterology* **126:** 1574–1581
60 Srinivasan R (2001) Infliximab treatment and pregnancy outcome in active Crohn's disease. *Am J Gastroenterol* **96:** 2274–2275
61 Mahadevan U *et al.* (2005) Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease. *Aliment Pharmacol Ther* **21:** 733–738
62 Vasiliauskas E *et al.* (2005) High serum levels of infliximab detected in the newborn of a mother receiving infliximab during pregnancy. *Gastroenterology* **128 (Suppl):** 128
63 Meadows M (2001) Pregnancy and the drug dilemma. *FDA Consumer* **35:** [http://www.fda.gov/fdac/features/2001/301_preg.html] (accessed 1 February 2006)